REMARKS

Restriction Requirement

The Examiner has acknowledged applicants' election of Group II (Claims 11-14) and species B (anti-CD40L antibodies). With respect to applicants' traversal of the species, the Examiner notes that inventions must be either independent or distinct and a burden on the Examiner if restriction is required. However, although the Examiner has stated that the inventions are distinct, he still has not indicated whether there would be a serious burden on the Examiner. Thus, it is not clear that the restriction is proper. However, in order to speed prosecution, applicants acknowledge that the requirement has been made final.

Claim Amendments

Claims 12, 13 and 23 have been canceled. Claims 11, 14, 22, 24, 26 and 27 have been amended as described below. Claim 28 has been added. The amendments and new claim cover the same invention as the pending claims, differing only in scope. No additional searching is necessary.

Claims 11, 14, 22 and 24 were amended to replace the term "comprising" with the term "consisting essentially of", and to recite components of the compositions and kit. New Claim 28 is directed to a kit, consisting of components similar to those recited in amended Claim 22. Support for the amendments and new claim is found, for example, in Claims 11, 13 and 14 as originally filed and on page 12, lines 5-8, page 13, lines 4-8, and page 14, line 13 of the Specification.

Claim 26 was amended to replace the claim terms immunosuppressive agents, apoptosis agents, agonistic agents and antagonistic agents, with the terms steroids, cytotoxic drugs, fungal and bacterial derivatives and antibodies. Support for this amendment is found on page 13, lines 4-8 of the Specification.

Claim 27 was amended to be independent and to recite a composition comprising two active ingredients, wherein the active ingredients consist of rapamycin, a biologically active derivative thereof, and at least one costimulation blockade agent. Support for this amendment is found on the Specification on page 12, lines 8-11 and in Claims 11 and 13 as originally filed.

No new matter has been added.

Formal Drawings

The request for correction of informalities is acknowledged. If necessary, a formal figure will be submitted upon allowance of the claims.

Withdrawal of Enablement Rejection under 35 U.S.C. § 112, First Paragraph

Applicants respectfully acknowledge withdrawal of the enablement rejection of Claims 11, 12 and 14.

Written Description Rejection of Claim 26 under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claim 26 on the grounds that the specification does not provide adequate written description of the claimed invention, namely immunosuppressive agents, apoptosis agents and antagonistic agents, because identifying characteristics such as structure or other physical and/or chemical characteristics are not set forth in the specification as filed. The Examiner states that the applicants are claiming a broad generic class of molecules/agents in the absence of the support of the disclosure of a limited representative number of species. The Examiner also states that a mere idea or function is insufficient for written description, and that isolation and characterization are required.

Claim 26 has been amended. As amended, the claim is directed to a composition consisting of rapamycin or a derivative, a costimulation blockade agent, and a member of a disclosed Markush group, specifically, physiological carriers, vehicles, steroids, cytotoxic drugs, fungal derivatives, bacterial derivatives, antibodies and fish oil.

These claim terms fall squarely in the rule dictated in *In re Herschler*, *Rasmussen* and *In re Smythe,* cited in the Guidelines for Examination of Patent Applications under 35 U.S.C. 112, paragraph 1, "Written Description Requirement", referenced by the Examiner. Copies of these cases are attached hereto as Exhibits 1-3 for the Examiner's convenience.

In *In re Herschler*, the process claims recited "physiologically active steroidal agents", a phrase not found in the great-grandparent application. 200 U.S.P.Q. 711 (CCPA 1979). The court found that the earlier application complied with the written description requirement for the claims even though the application only exemplified a single species of agents. The court noted that it was necessary only that the application describe the limitations so that one of ordinary skill would recognize from the disclosure that the applicants invented processes including those limitations. *Id.* at 717. The court distinguished the case from one in which the claims were drawn to novel steroidal agents themselves. *Id.* The *Herschler* court concluded:

> claims drawn to the use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds. Occasionally, a functional recitation of those known compounds in the specification may be sufficient as that description. ...[Here,] such is the case. *Herschler*, 200 U.S.P.Q. at 718.

Similarly, in *In re Rasmussen*, the applicants amended a method claim by substituting "adheringly applying" for language specifying application with adhesives. 211 U.S.P.Q. 323, 325 (CCPA 1981). The specification only disclosed an example which was directed to adheringly applying with adhesive. The Court found that the claim complied with the written description requirement, because one skilled in the art who read the specification would understand that it is not important how the layers were adhered, so long as they were adhered. *Id.* at 327.

Finally, in *In re Smythe*, claims were amended to recite "an inert fluid", although the Specification disclosed the use of "air or other gas which is inert to the liquid". 178 U.S.P.Q. 279, 284 (CCPA 1973). The court stated that "we cannot agree with the broad proposition ... that in every case where the description of the invention in the Specification is narrower than that in the claims there has been a failure to fulfill the description requirement in section 112." *Id.* The court determined that the broader concept of "inert fluid" would naturally occur to the skilled artisan from reading the description of the use and functions of the media specifically described, even though the term "inert fluid" did not appear in the specification.

In contrast, the *Eli Lilly* court stated that, for claims directed to novel genetic material, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA", without more, is not an adequate written description of the genus, because it does not distinguish the claimed genus from others, except by function. 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997). A definition of a gene by function does not suffice to define the genus of a gene because it is only an indication of what the gene does, not what it is, and many genes may achieve the same result. *Id.* at 1406. Thus, a functional definition does not specifically define *any* of the genes that fall within the definition, or define any structural features commonly possessed by members of the genus that distinguish them from others. Thus, the court noted that adequate written description of DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention. *See also Colbert v. Lofdahl*, 21 U.S.P.Q.2d 1068, 1071 (BPAI 1992) (claim directed to a recombinant molecule).

Like the applicants in *Rasmussen, Herschler* and *Smythe*, the applicants are not attempting to claim a novel substance, but, rather, are reciting substances based on their properties in combination with rapamycin (or a derivative) and a costimulation blockade agent.

Thus, Claim 26, particularly as amended, is sufficiently supported by the specification to satisfy the written description requirement. Reconsideration and withdrawal of this rejection are respectfully requested.

Withdrawal of Rejection of Claims 11, 13 and 14 under 35 U.S.C. § 102(e) and Claims 11-14 under 35 U.S.C. § 103(a)

Applicants acknowledge withdrawal of the previous rejection of Claims 11, 13 and 14 under 35 U.S.C. § 102(e) as anticipated by de Boer et al. (U.S. Patent No. 5,869,050 or 5,747,034). Applicants also acknowledge withdrawal of the previous rejection of Claims 11-14 under 35 U.S.C. § 103(a) as being unpatentable over de Boer et al. (U.S. Patent Nos. 5,869,050 and/or 5,747,034) in view of Kelly et al. (U.S. Patent No. 5,118,493).

Rejection of Claims 11, 13, 14, 22 and 24-27 under 35 U.S.C. § 102(e)

Claims 11, 13, 14, 22 and 24-27 are rejected under 35 U.S.C. § 102(e) as anticipated by Chen et al. (U.S. Patent No. 5,990,109). Claim 13 has been cancelled. According to the Examiner, Chen et al. disclose compositions comprising at least CD40L-specific antibodies and immunosuppressive agents comprising rapamycin. The Examiner states that Applicants' arguments, filed 3/29/02, have been fully considered but are not found convincing essentially for the reasons of record.

As stated in the previous response, Chen et al. teach compositions comprising at least heterocyclo-substituted imidazopyrazine compounds and compositions, for use as protein tyrosine kinase inhibitors. Chen et al. do not disclose or claim compositions which do not also include heterocyclo-substituted imidazopyrazine compounds. Moreover, Chen et al. do not disclose kits of any kind. Chen et al. do not disclose compositions comprising CD40L-specific antibodies and immunosuppressive agents as active and essential ingredients.

The Examiner states that "it is noted that the claimed methods recite 'comprising' which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See M.P.E.P. § 2111.03. Therefore, the claims can encompass heterocyclo-substituted imidazopyrazine compounds." (page 7 of Office Action). Applicants' amended claimed compositions and kits do not comprise the heterocyclo-substituted imidazopyrazine compounds disclosed in Chen et al. as active ingredients.

Claims 11, 14, 22 and 24 have been amended to recite compositions and kits "consisting essentially of" specific components recited in the claims. Claim 25 also recites the transitional phrase "consisting essentially of". This phrase "limits the scope of the claim to the specified

materials or steps 'and those that do not materially affect the basic and novel characteristics' of the claimed invention." M.P.E.P. §2111.03. The Specification provides a clear indication that the basic and novel characteristics of the claimed invention are provided by rapamycin, or a biologically active derivative, and a costimulation blockade agent.

Claim 26 recites a composition "consisting of" specified components. Claim 27 is directed to a composition comprising active ingredients which consist of rapamycin or a derivative and at least one costimulation blockade agent. Since heterocyclo-substituted imidazopyrazine compounds are not active or essential ingredients of the claimed compositions and kits, the claims are not anticipated by Chen et al. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection of Claims 11, 13, 14, 22 and 24-27 under 35 U.S.C. § 102(e)

Claims 11, 13, 14, 22 and 24-27 are rejected under 35 U.S.C. § 102(e) as anticipated by Nadler et al. (U.S. Patent No. 5,962,415). Claim 13 has been cancelled. According to the Examiner, Nadler et al. disclose compositions comprising at least CD40L-specific antibodies and immunosuppressive agents comprising rapamycin.

The Examiner states that applicants' arguments, filed 3/29/02, have been fully considered but are not found convincing essentially for the reasons of record. According to the Examiner, applicants state in their response to the Office Action that "Nadler et al. does not disclose compositions comprising CD40L-specific antibodies, nor compositions comprising rapamycin." This is an incorrect statement of applicants' argument. In fact, applicants expressly stated that "Nadler et al.'s compositions comprise polypeptide inhibitors of nuclear translocation of a cytoplasmic protein and an immunosuppressant, such as rapamycin. (Column 1, lines 1-5; column 3, lines 6-25; column 14, lines 45-51)."

Nadler et al. do not disclose compositions comprising CD40L-specific antibodies. The Examiner states that "Nadler et al. does teach that the inhibitors of gp39 (i.e. CD40L) can take the form of antibody component peptides (see column 8, lines 30-33 and 39)." Applicants respectfully disagree. Nadler et al. discloses:

> Thus, inhibition of immune responses by the compositions of the present invention can take the form of: inhibition of antibody production, including the production of antibody component peptides such as K light chain polypeptide; inhibition of cytokine production, including such cytokines as interleukin-1, interleukin-2, interleukin-4, interleukin-6, interleukin-10, tumor necrosis factor, or granulocyte-macrophage colony-stimulating factor; and/or the inhibition of the expression of cell-surface receptors such as an interleukin-2 receptor, gp39, CD40, CD45, CD80, CD86, ICAM, ELAM, major histocompatibility complex ("MHC") class II, or VCAM. Clark et al. (1994) Nature

367:425. (Column 8, lines 30-41)

Thus, Nadler et al. disclose that the inhibition of immune responses by their compositions can take the form of *inhibition of antibody production, including inhibition of production of antibody component peptides* and *inhibition of the expression* of cell-surface receptors such as gp39 and CD40. (Column 8, lines 30-41). They do not state that the inhibitors can take the form of antibody component peptides.

Nadler et al. do not disclose the applicants' compositions and kits, which comprise at least one costimulation blockade agent such as anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof.

Moreover, as noted above, Claims 11, 14, 22 and 24 as amended, and Claim 25, recite the transitional phrase "consisting essentially of", and Claim 26 recites "consisting of". The scope of these claims does not encompass compositions and kits comprising Nadler et al.'s compounds. Claim 27 is directed to a composition wherein the active ingredients consist of rapamycin, or a derivative thereof, and a costimulation blockade agent. Because Nadler et al.'s compounds cannot be active ingredients of the composition, they are not encompassed within the claim. None of the claims encompass the compounds recited by Nadler et al. (polypeptide inhibitors of nuclear protein translocation) as active or essential components of the disclosed compositions or kits. All of the compositions disclosed by Nadler et al. do include these compounds.

Therefore, the Nadler et al. reference does not anticipate the claims. Reconsideration and withdrawal of this rejection are respectfully requested.

Rejection of Claims 11-14 and 22-27 under 35 U.S.C. § 103(a)

Claims 11-14 and 22-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Noelle et al. (U.S. Patent No. 5,942,229) in view of Chen et al. (U.S. Patent No. 5,990,109) and/or Nadler et al. (U.S. Patent No. 5,962,415) and further in view of Kelly et al. (U.S. Patent No. 5,118,493). Claims 12, 13 and 23 have been cancelled. As stated above, Claims 11, 14, 22, 24 26 and 27 have been amended. These amended claims, and Claim 25, exclude the compounds of Chen et al. and Nadler et al., because these compounds are not active or essential compounds of the claimed compositions and kits.

The teachings of Chen et al. and Nadler et al. are focused on the mechanisms of specific compounds which are not encompassed in applicants' claims. Chen et al. teach compositions comprising at least heterocyclo-substituted imidazopyrazine compounds, for use as protein tyrosine kinase inhibitors, and Nadler et al. teach compositions comprising polypeptide inhibitors

of nuclear protein translocation. These inhibitors do not share the same properties of applicants' claimed costimulation blockade agents. As stated in the previous amendment, in an obviousness analysis, a proposed modification of a prior art reference cannot change the principle of operation of the reference (M.P.E.P. § 2143.01). The Examiner asserts that the references teach that compositions comprising inhibitors, including immunosuppressive agents, can be combined. However, as discussed above, the claimed compositions and kits, particularly as amended, do not encompass these inhibitors as active or essential components.

According to the Examiner, the prior art taught that both rapamycin and CD40L-specific antibodies were useful as immunosuppressants, including the inhibition of graft rejection. However, neither Chen et al. nor Nadler et al. teach or suggest combining compositions comprising rapamycin and their inhibitors with the claimed CD40/CD40L antagonists to achieve lasting graft tolerance. The Examiner states that Noelle et al. provides the expectation of success and motivation that CD40L-specific antibodies are a key ingredient of immunosuppressive formulations. However, Noelle et al. do not teach or suggest combining such antagonists with rapamycin.

To establish a prima facie case of obviousness there must be a suggestion or motivation in the references or in the knowledge available to one of ordinary skill in the art to combine the references. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicants' disclosure. Impermissible hindsight must be avoided. M.P.E.P. §§ 2142 and 2143. Furthermore, nonobviousness can be established by such unexpected results. See M.P.E.P. § 716.02(a). "Expressions of disbelief by experts constitute strong evidence of nonobviousness". M.P.E.P. § 716.03.

Applicants' invention relates to the discovery that rapamycin does not block the IL-2 dependent activation-induced cell death required for enduring tolerance. As stated in the application, prior to applicants' invention, many experts believed that immunosuppressive agents could not be administered with costimulation blockade agents to achieve permanent engraftment. Thus, one of skill in the art would not have been motivated to combine references teaching compositions comprising rapamycin with the teachings of Chen et al. (compositions comprising at least heterocyclo-substituted imidazopyrazine) or Nadler et al. (compositions comprising polypeptide inhibitors of nuclear protein translocation) and with Noelle et al. (compositions comprising gp39 antagonists and soluble CTLA-4 or an IL-4 inhibitor) or Kelly et al. (compositions comprising fish oil) to practice the claimed invention with a reasonable expectation of successfully achieving lasting graft tolerance.

Thus, the invention would not have been obvious at the time the invention was made to one of ordinary skill in the art. Reconsideration and withdrawal of this rejection to these claims are respectfully requested.

CONCLUSION

The claims are now in condition for allowance. Thus, the Examiner is respectfully requested to reconsider the rejections and to withdraw them.

If the Examiner feel that a telephone conversation with Applicants' attorney would be helpful in expediting the prosecution of this case, the Examiner is encouraged to call Applicants' Attorney at (978) 341-0036.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

11. (Twice Amended) A composition [comprising] consisting essentially of:

(a) rapamycin, or a biologically active derivative thereof [, and];

(b) at least one costimulation blockade agent[, wherein the costimulation blockade agent comprises at least one agent] selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof; and

(c) at least one member selected from the group consisting of physiological carriers, vehicles and fish oil.

14. (Twice Amended) A kit [comprising at least one costimulation blockade agent and] consisting essentially of:

(a) rapamycin, [wherein the costimulation blockade agent comprises] or a biologically active derivative thereof;

(b) at least one costimulation blockade agent selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof; and

(c) at least one member selected from the group consisting of physiological carriers, vehicles and fish oil.

22. (Amended) A composition [comprising] consisting essentially of:

(a) rapamycin, or a biologically active derivative thereof[, and];

(b) at least one costimulation blockade agent [, wherein the costimulation blockade agent comprises at least one agent] selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof; and

(c) at least one member selected from the group consisting of physiological carriers, vehicles, corticosteroids, azathioprine, cyclophosphamide, cyclosporine, FK506, rapamycin, antibodies to lymphocytes, and fish oil.

24. (Amended) A kit [comprising] consisting essentially of:

(a) rapamycin, or a biologically active derivative thereof[, and];

(b) at least one costimulation blockade agent [comprising at least one agent] selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof; and

(c) at least one member selected from the group consisting of physiological carriers, vehicles, steroids, cytotoxic drugs, fungal derivatives, bacterial derivatives, antibodies and fish oil.

26. (Amended) A composition consisting of:

(a) rapamycin, or a biologically active derivative thereof;

(b) at least one costimulation blockade agent selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof; and

(c) at least one member selected from the group consisting of physiological carriers, vehicles, [immunosuppressive agents, apoptosis agents, agonistic agents, antagonistic agents] steroids, cytotoxic drugs, fungal derivatives, bacterial derivatives, antibodies and fish oil.

27. (Amended) [The] A composition [of Claim 11,] comprising two active ingredients, wherein the active ingredients [of the composition are] consist of rapamycin[,] or a biologically active derivative thereof, and at least one costimulation blockade agent, wherein the costimulation blockade agent comprises at least one agent selected from the group consisting of anti-CD40 antibodies, anti-CD40L antibodies, CD40-Ig, CD40L-Ig, and soluble extracellular domain proteins of CD40 and CD40L and derivatives thereof.